Title: The effects of exercise on cardiovascular disease risk factors and cardiovascular physiology in rheumatoid arthritis.

Abstract

Cardiovascular disease (CVD) morbidity and mortality is highly prevalent in patients with rheumatoid arthritis (RA) with debilitating effects for the individual as well as significant healthcare impact. Current evidence demonstrates that engaging in aerobic and resistance exercise (i.e. structured physical activity) can significantly improve patient-reported and clinical index-assessed outcomes in RA. In addition to this, engagement in exercise programs improves, in a dose-dependent manner, the risk of developing CVD as well as CVD symptoms and outcomes. The present narrative review uses evidence from systematic reviews and meta-analyses as well as controlled trials, to synthesize the current state-of-the-art on the potential effects of aerobic and resistance exercise on CVD risk factors as well as on cardiac and vascular function and structure in people with RA. Where there is a lack of evidence in RA to explain potential mechanisms, relevant studies from the general population are also discussed and linked to RA.

Key words: exercise, physical activity, rheumatoid arthritis, non-communicable disease, autoimmune disease, cardiovascular disease, inflammation, rehabilitation

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition characterized by symptoms, such as joint inflammation, pain and fatigue, contributing to functional disability and having detrimental effects on the quality of life of the people affected. RA is also characterized by systemic manifestations, including lung, skin, ocular and neurological involvement [1]. Most notably, over the last years it has been established that the incidence of cardiovascular disease (CVD) in the context of RA has increased [2]. A 2012 meta-analysis of observational studies that took onto consideration for analyses only the first CVD event during follow-up (data from 41.490 RA patients with no history of CVD prior to RA onset) revealed that the CVD incidence in RA is 48% (68% for myocardial infarction and 41% for cerebrovascular accidents); accurate estimates for heart failure were not available due to lack of data [3] but this is also thought to be increased in RA [4]. The potential contributors to the increased CVD risk in RA are multiple and may include increased prevalence of traditional CVD risk factors (such as obesity, dyslipidemia and hypertension) as well as the persistent inflammatory load that accompanies RA, and their sequelae, i.e. vascular dysfunction. As a result, considerable efforts have focused on developing recommendations to mitigate the detrimental effects of the increased CVD incidence in RA, such as the recent updated recommendations by European League Against Rheumatism (EULAR) [5].

Based on the accumulated evidence to date, increasing physical activity and/or engaging in aerobic and resistance exercise programs are effective interventions to significantly reduce CVD risk in RA [6, 7]. Given the high incidence of CVD in RA and the multiple different beneficial effects of exercise on CVD outcomes, the present review aims to describe the effects of exercise on CVD risk factors as well as the overall functional and structural cardiac and vascular physiological adaptations in RA.

Search methodology

This is a present narrative review which has not utilized a systematic review approach. However, we have still followed suggested evidence-based approaches to synthesize this review [8]. In specific, the studies to synthesize the arguments within the present review were predominantly based from systematic reviews and meta-analyses published in the Cochrane Library. Where relevant studies were not available in this data source, we have retrieved systematic reviews and meta-analyses, individual randomized and/or controlled trials (or in the absence of such studies, we retrieved epidemiological studies) from Medline/Pubmed. We have not used the Patient Intervention Comparison Outcome (PICO) tool, since the present review retrieved studies from the general population, population with different non-communicable diseases as well as rheumatic and musculoskeletal diseases (RMDs).

Physical activity and exercise

Physical activity is any bodily movement that produces contraction of the muscles and increases energy expenditure above resting levels. Exercise is only part of a person's overall physical activity levels, which needs to be structured and planned. There is some evidence in the general population and specific sub-populations to suggest that the beneficial effects of physical activity and exercise on various health outcomes are dose-dependent [9]. This means that the different intensities that can be applied through an exercise program can have different effects on human physiology (and thus the beneficial effects on different health outcomes) depending on whether the intensity will be light, moderate or vigorous. The present review focuses on the effects of exercise rather than overall physical activity in people with RA; it will also focus on the effects of aerobic and resistance types of exercise rather than any other training regimens while also reporting the intensity, where available and/or necessary.

Aerobic and resistance type of exercise represents a significant stimulus within the human body. In response to the increased physiological and metabolic demands imposed by aerobic and resistance exercise, the human body needs to acutely and rapidly adapt and alter resting physiological process, to meet the increased exercise-induced physiological demands. This process is characterized by marked changes, including increased oxygen uptake and oxygen delivery to the exercising muscles accompanied by increased cardiac and pulmonary function with the synergy of the vasculature. These repeated and acute changes result in long term physiological adaptations which are necessary to accommodate the requirements of repeated aerobic and resistance exercise training and are characterized by both functional and structural changes in different physiological systems, including the cardiovascular, metabolic and respiratory systems. The insisting presence of inflammatory load and functional disability in RA vs. the normal population may accelerate processes that lead to increased risk for comorbidities (e.g. CVD risk). However, it must be noted that exercise provides a stimulus for specific beneficial adaptation in humans, irrespective of the presence of a non-communicable disease and/or condition. In support of this, the cardiorespiratory improvements seen in the healthy population vs. RA patients may be more pronounced after a certain training period for specific outcomes, however, research studies still demonstrate

significant improvements in RA patients in both disease-related and patient-important outcomes [10].

The numerous different beneficial health adaptations that take place in response to repeated engagement in aerobic and resistance exercise are now widely recognized. As a result, exercise engagement is now a most important part of public health strategies not only for the normal population but more importantly, in populations with non-communicable diseases, including RA. EULAR has now published specific recommendations for frontline healthcare practitioners promoting the inclusion of physical activity and exercise as part of routine clinical practice, aiming to improve the management of disease symptoms and reduce CVD risk in people with rheumatic and musculoskeletal diseases [11].

Effects of exercise on atherosclerosis and inflammation

Atherosclerosis is a process of accumulation of lipids and fibrous elements in the endothelium (tunica intima), predominantly in large coronary arteries [12]. Atherosclerosis is modulated by inflammatory processes throughout its development (endothelial activation, foam-cell formation and decreased cholesterol efflux, and plaque destabilization). It has been hypothesized that the long-term inflammatory load in chronic inflammatory conditions, such as RA, may promote an accelerated atherosclerotic process and be associated with earlier sub-clinical or clinically overt manifestations and worse outcomes in such conditions [13]. Exercise seems to be able to partly reverse the following specific biological/physiological processes that associate with the atherosclerotic process.

Improved lipid profile

Research in non-RA populations suggests that exercise has beneficial effects on lipid profiles. An umbrella 2014 review – which included both meta-analyses and randomized controlled trials – on the effects of exercise on lipids, revealed significant exercise-induced beneficial effects on lowering total cholesterol levels in populations that did not receiving cholesterol-lowering medication [14]. Results from another meta-analysis on adults with the metabolic syndrome (seven trials with 206 participants of which 128 in the exercise group) revealed that these effects seem to be predominantly due to aerobic endurance exercise increasing high density lipoprotein (HDL) rather than lowering low density lipoprotein (LDL) [15]. Exercise, particularly when maintained for more than four weeks, can also reduce triglyceride levels in males and females >18yrs in the general population [16, 17].

Although there is a lack of equivalent large studies and meta-analyses on the effects of exercise on lipids specifically in RA, lipids have been investigated in relevant studies as a secondary outcome. Observational studies reveal that RA patients that engage in more physical activity and have better cardiorespiratory fitness levels – i.e. the ability of the cardiovascular and respiratory systems to supply oxygen to exercising muscles – have a better lipid profile (mainly higher HDL) compared to those RA patients who do not exercise [18, 19]. In line with these data, in a controlled trial of a six-month aerobic and strength exercise program vs. no exercise in people with RA, triglycerides were significantly reduced and HDL was significantly increased [20]. The specific physiological mechanisms for these

exercise-induced benefits in RA are still unclear. However, possible mechanisms arise from work in other populations without history of CVD. In specific, in response to exercise, skeletal muscles enhance their ability to increasingly utilize lipids, thereby reducing plasma lipid levels [21]. This is probably because exercise may increase lecithin-cholesterol acyltransferase, which is the enzyme responsible for ester transfer to HDL [22], which is mainly increased following exercise [23]. Moreover, exercise increases the activity of lipoprotein lipase, which hydrolyses triglycerides and also acts as a ligand/bridging factor for lipoprotein uptake [24]. It should be noted, however, that these effects may be depended on the intensity and frequency of exercise. Even in the general population, available data in this area are still immature and therefore, definitive conclusions cannot be drawn.

Reduced oxidization of low-density lipoprotein and oxidative stress

A necessary mechanism for the development of atherosclerosis is the oxidation of LDL, which then contributes to the formation of foam cells [12]. Although preliminary, currently available data indicate that, in normal and obese populations, LDL oxidation could be reduced in response to exercise thus, halting the progression of the atherosclerotic process [25, 26]. On the other hand, oxidative stress also contributes to the development of atherosclerosis and thus, to CVD. A 2017 meta-analysis (30 trials and 1346 healthy participants) revealed that increasing exercise participation reduces pro-oxidant parameters along with improving the body's anti-oxidant capacity, thereby reducing the negative effects of oxidative stress [27]. Studies investigating the oxidative stress response to exercise in RA are scarce. A product of tyrosine nitration mediated by reactive oxygen species, 3-nitrotyrosine, has been found to be decreased after three months of exercise training in RA patients [28]. These data, however, are preliminary and need to be confirmed in appropriately designed trials.

Inflammation

The inflammatory process requires key pro-inflammatory cytokines, namely interleukins 1 and 6 (IL-1 and IL-6) and tumour necrosis factor alpha (TNFa), to work synergistically and cross-talk to initiate the acute phase response. In addition, the progression of atherosclerosis necessitates that inflammatory processes take place [12]. However, the phenotypes that characterize the kinetics of these key cytokines during inflammation and exercise, are significantly different.

In healthy adults, IL-6 mRNA increases in a dose-dependent manner in response to exercise [29]. However, the overexpression of IL-6 during exercise is induced by muscle contraction and is not macrophage-driven, i.e. what is seen in the inflammatory processes. The actions of the overexpressed IL-6 in exercise and inflammation also differ. Rather than to initiate and progress the inflammatory response, the depleted intra-muscular energy during exercise results in the increase in IL-6 to act as a "trigger" for lipolysis and hepatic glycogenolysis and thus, to direct more energy into the energy-depleted exercising muscle [30]. The non-inflammatory phenotype of the exercise IL-6 induction is also supported by the fact that, in inflammation, IL-1 and TNFa are overexpressed, while during and post-exercise, the same cytokines remain suppressed. Furthermore, other cytokines with anti-inflammatory actions, such as soluble TNF receptor, interleukin 10 as well as IL-1 receptor antagonist also

elevate during and post exercise [29]. It can thus be argued that overall, in non-RA populations, during and after an exercise bout/session, the human body creates an anti-inflammatory environment.

Adipocytes (cells of the adipose tissue) are a known trigger of biological pathways that promote the inflammatory response [31]. In line with this, increased adiposity (i.e. overweight and obese individuals) associates with higher inflammatory load compared to the general population; studies also reveal that inflammatory processes are activated early in adiposity expansion and progression [32]. A recent systematic review and meta-analysis of 117 studies and 4,815 adults with a body mass index of $\geq$25 $kg \cdot m^{-2}$, investigating the effects of exercise vs. hypocaloric diet on adiposity, suggested that, in the absence of weight loss, exercise results in greater loss of visceral fat [33]. Reducing the size of adipocytes as a result of exercise, results in lower levels of inflammation, even in populations with non-communicable, low-grade inflammatory diseases, such as diabetes [34]. It is therefore thought that in non-RA populations, the long-term anti-inflammatory effects of exercise are mainly mediated via the reduction in the size of adipocytes.

Surprisingly, exercise and inflammatory load in RA has only been investigated as a secondary outcome with conflicting findings. For aerobic training, a single-arm pilot study utilizing a high-intensity walking intervention for 10 weeks resulted in significant reductions in erythrocyte sedimentation rate and number of swollen joints [35], however, results from relevant randomised controlled trials are not in line with this and did not observe similar reductions in the same parameters [36]. The conflicting findings with regards to aerobic training on inflammation (ESR or CRP levels) in RA are also evident in the 2009 Cochrane Library meta-analysis on exercise and RA [10]. In contrast, a systematic review and meta-analysis on strength training, identified three studies (pulled results from 133 RA patients and 125 RA controls) that investigated ESR as a secondary outcome, revealed significant reductions in this marker of inflammation; no data were available for other parameters of inflammatory load [37]. Importantly, none of the above trials have directly investigated the link between inflammation with CVD outcomes and therefore, the evidence of such associations/effects requires further investigation in RA.

Effects of exercise on other classical CVD risk factors

Hypertension

Hypertension is highly prevalent in RA patients, however, in clinical practice is often underdiagnosed and undertreated [38, 39]. Elevated blood pressure represents a risk factor for CVD that can be reduced via exercise participation by a clinically significant magnitude in healthy adults [40]. Although medication can achieve higher reductions in blood pressure compared to exercise, a 2018 network meta-analysis of 391 randomized controlled trials, demonstrated a consistent reduction in systolic blood pressure, especially in hypertensive individuals [41].

Studies investigating blood pressure responses to exercise do exist for RA. Observational studies suggest that higher levels of exercise and cardiorespiratory fitness associate with lower systolic blood pressure [18, 19]. A controlled study of combined aerobic

and strength training vs. no exercise showed a significant reduction in both systolic and diastolic blood pressure [20]. However, the exact mechanisms for this phenomenon in this population have still to be identified. In general, the physiological mechanisms by which exercise can reduce blood pressure are multiple and have been studied in the general population but not RA; these include reduced peripheral vascular resistance, increased nitric oxide bioavailability as well as enhanced baroreceptor sensitivity [42].

Insulin Resistance

Insulin resistance is also highly prevalent in RA compared to non-RA controls, up to 31% [43]. Exercise is a cornerstone adjunct intervention for managing insulin resistance, a fact that has led the American Diabetes Association to publish a Position Statement promoting the use of exercise for – predominantly – managing type II diabetes [44]. The mechanisms that are thought to contribute to lower insulin resistance in response to exercise are via enhancing the translocation of the insulin-mediated glucose transporter type 4 (GLUT-4, an insulin regulated glucose transporter), that translocates from intracellular storage depots to the plasma membrane and T-tubules after exercise-induced muscle contraction. In healthy adults, the GLUT-4 translocation results in increased glucose uptake after the termination of an exercise session, and may last up to 24h [45]. In line with this, a recent Cochrane Library meta-analysis reveals that both aerobic and resistance training have statistically and clinically significantly effects on glycaemic control in type II diabetes [46]. These findings are partly corroborated in research on RA patients: higher physical activity and cardiorespiratory fitness levels associate with reduced insulin resistance in RA [18, 19] however, these findings have to be confirmed in appropriately designed, controlled trials.

Obesity

Obesity is now considered a real threat for public health and a strong risk factor associated with the development of non-communicable diseases, including CVD. Increased size of adipocytes (obesity phenotype) leads to insulin resistance as well as inflammation, which are important biological processes promoting disturbed physiological homeostasis [31]. Apart from energy storage, adipose tissue is now considered an endocrine and paracrine organ, secreting bioactive molecules called adipokines. Adipokines influence the inflammatory process by modulating aspects of the innate / adaptive immunity promoting a pro-inflammatory state [47, 48], by enhancing the production of key pro-inflammatory cytokines, such as IL-1, IL-6 and TNFa, which are key molecules in the development and progression of both RA and CVD [49]. Due to the debilitating RA symptomatology which includes fatigue and functional disability, patients with RA tend to be more sedentary, which may be one of the main reasons why obesity and overweightness are more prevalent in this patient population compared to normal controls [47]. Studies in RA have demonstrated that obesity associates independently with CVD risk factors [50] and is a potential drive of the inflammatory state in RA [51]. As such it comes as no surprise that obesity may lead to a significantly higher 10-year CVD risk event probability in RA [52].

Exercise may reduce adiposity, in a dose-dependent manner, however it must be noted that these findings derive from the general as well as overweight/obese populations. A 2016 meta-analysis (117 studies with 4815 adults with a body mass index $\geq$ 25 $kg \cdot m^{-2}$)

investigating the effects of exercise vs. hypocaloric diet, revealed that in the absence of weight loss, increasing exercise can reduce visceral fat to a greater extend compared to dieting [33]. Another 2015 meta-analysis, in obese and overweight individuals, concluded that diet interventions require the contribution of exercise to elicit beneficial changes in body composition (i.e. reduced adiposity) and obesity-related metabolic biomarkers; the same study demonstrated that strength / resistance training in combination with a hypocaloric diet was more effective to improve body composition compared to other interventions [53].

An overview of the exercise-induced physiological mechanisms on CVD risk factors and processes of atherosclerosis, appears in Figure 1.

******* Figure 1 around here *******

Rheumatoid Cachexia

An important systemic manifestation and underdiagnosed condition in RA, is rheumatoid cachexia, a condition characterized by increased fat deposition and reduced muscle mass, while weight remains unchanged [54, 55]. Rheumatoid cachexia potentially develops due to two main reasons:

a) Increased expression of TNFa that promotes proteolysis via the activation of nuclear factor-kappa B (NF- κB); NF-κB can result in the overexpression of the ubiquitin-proteasome system that in turn, can degrade muscle proteins [56]. Moreover, NF-κB can also promote the expression of inflammatory cytokines that directly or indirectly promote muscle-wasting while it can also inhibit processes of myogenic differentiation [57] which are necessary for the regeneration of atrophic muscles, such as those seen in RA.

b) Physical inactivity which results in increased fat deposition and reduced muscle mass.

This profound change in body composition seen in RA, may contribute to the progression of a CVD phenotype due to the increased fat deposition [55]. However, more research is required to establish these associations and/or effects as well as the exact prevalence of rheumatoid cachexia based on appropriate diagnostic criteria (53). It is worth noting, nevertheless, that the effects of rheumatoid cachexia (muscle wasting) may contribute to the lack of exercise in RA, further increasing the risk of CVD [55, 58].

Effects of exercise on cardiac and vascular structure and function

Aerobic and resistance exercise training results in beneficial changes in cardiac and vascular structure and function. The current knowledge around these beneficial exercise-induced changes derives from areas of sport science (i.e. effects of exercise on athletes). In contrast, studies in RA have investigated the effects of RA on different cardiac/vascular structural and

functional changes as part of the disease presence and progression, with only one study available in relation to exercise in RA.

Cardiac Function and Structure

The exercise-induced cardiac adaptations can be characterized as structural, functional as well as related to the electrical activity of the heart. These beneficial aerobic and resistance effects of exercise have led to the use of the term "athlete's heart" which indicates the marked changes in the heart of athletes when compared to non-active and/or sedentary counterparts. A 2013 meta-analysis of 92 prospective studies in athletes (84 on echocardiography and 17 on magnetic resonance imaging) on exercise-induced cardiac changes, revealed larger left ventricular structures in endurance and resistance-trained athletes [59]. Relevant studies in RA are currently missing and therefore, relevant conclusions cannot be drawn for this population.

RA develops at a later age in life, which coincides with unfavourable structural and functional changes in the heart. In addition to this, the increased prevalence of CVD risk factors seen in RA, places this population at an increased risk for CVD morbidity and mortality. Ageing *per se* results in changes in cardiac structure (left ventricular enlargement to compensate the loss of cardiomyocytes, atrial hypertrophy and dilatation) and function (electrical dysfunction, reduced left ventricular diastolic function and indirect systolic dysfunction through decreased myocardial contractility) [60]. However, involvement in exercise has been found to associate with slowing down the ageing-related effects of cardiac dysfunction. Veteran endurance athletes demonstrate larger absolute and indexed right and left ventricular end-systolic and end-diastolic volumes, stroke volume as well as wall thickness compared to age-matched non-athletic controls [61]. The biological mechanisms characterizing pathological cardiac hypertrophy, a potential sign of compromised heart function leading to heart failure, are different from those induced by exercise; the latter changes are associated with enhanced cardiac function. A summary of the exercise-induced mechanisms in the hearts' structure and function, appears in Figure 2.

The molecular mechanisms for the observed exercise-induced cardiac phenotypes are mediated via the insulin-growth factor 1 (IGF1), the phosphoinositide 3 kinase (PI3K), and protein kinase B (Akt) pathway (Figure 2). Inhibition of the IGF1-PI3K-Akt pathway is detrimental to the function of the myocardium and may lead to the development of CVD. Early research into the athlete's-heart revealed that IGF1 and PI3K activation associate with cardiac hypertrophy (non-pathological phenotype) in athletes [62]. The activation of PI3K also seems to mediate molecular cardiac adaptations via targeting the Akt (serine / threonine kinase), and predominantly the Akt1 isoform. Akt activation phosphorylates cytosolic, mitochondrial and nuclear targets that regulate the observed exercise-induced myocardial growth [63].

Studies examining the heart in RA also exist, however these are mainly observational studies comparing the heart structure function and structure differentiation between RA patients and non-RA controls. Patients with RA who are asymptomatic for CVD, demonstrate a compromised cardiac structure and function, when different cardiac – predominantly echocardiographic – outcomes have been investigated. Perhaps the most common phenomenon of compromised cardiac function in RA is diastolic dysfunction. Left

ventricular diastolic dysfunction is found in 45% of RA patients with no CVD symptoms compared to a significantly lower 20% of non-RA controls [64], an observation also confirmed by a meta-analysis of 25 studies in 1614 RA patients [65]. Although, RA-related pathways, such as RA duration and IL-6 have been independently associated with diastolic dysfunction in RA [66], more research is required to determine the exact physiological mechanisms around these observations. Other structural cardiac outcomes also seem to be compromised in RA. In specific, recent meta-analyses revealed increased absolute and indexed left ventricular mass in RA patients [16 case control studies, [67]] and that, almost half of CVD asymptomatic RA patients (10 case-control studies) demonstrate marked valvular (nodules, stenosis, calcification and insufficiency) as well as pericardial effusion [68].

Finally, an area of research which is worth mentioning, is cardiac strain. Cardiac strain is an echocardiographic method for measuring segmental as well as global myocardial deformation (i.e. during the cardiac cycle). Although still far from been realized within clinical practice for diagnostic purposes, the evaluation of systolic strains and strain rates is now emerging as an important assessment for non-communicable diseases that are characterized by impaired myocardial function. In RA, disease activity and severity associate with greater left ventricle strain as well as left ventricular longitudinal strain [69, 70]. These findings may hold promise in the identification of subclinical cardiac morbidity which may be present despite normal left ventricular ejection fraction, however, more research is required on this area.

******* Figure 2 around here *******

Unfortunately, no studies exist to date, that have investigated the associations and/or effects of exercise on cardiac function and structure in RA. Nevertheless, cardiorespiratory fitness – a very significant beneficial outcome that requires, at least in the short term, functional cardiac adaptations – significantly increases in response to exercise in RA with direct significant beneficial effects in patient- and clinically-important outcomes, such as functional ability and fatigue [10, 71]. The identification of the cardiac structural and functional mechanisms that determine these changes in RA is necessary, thus necessitating more research in this field. This can provide greater insights on how the exercise-induced adaptations can reverse and/or mitigate the adverse cardiac effects seen in RA.

Vascular function and structure

The endothelium which is considered a very active organ, lines the entire cardiovascular system and is involved in multiple functions, including inflammation, angiogenesis and regulation of vascular tone. The long-term term inflammatory load of RA, is thought to affect these processes, thereby, promoting an unfavourable CVD phenotype [72]. However, the most recent, yet now dated, systematic review on the effects of RA on vascular function (93 studies, of which 27 longitudinal and 57 cross-sectional) does not provide definite conclusions about the associations and effects of persistent inflammation on different aspects

of vascular function and structure in RA [73]. In general, disturbed vascular homeostasis, which is a silent process (i.e. characterized by a lack of physical symptoms) contributes to the development of and is thought to precede atherosclerosis. Nitric oxide is the main endothelium-derived regulator of vascular homeostasis; reduced nitric oxide synthesis and bioavailability promotes dysfunction via loss of basal vasodilator tone, enhanced blood cell migration and raised local chemokine and/or cytokine release, thereby promoting atherosclerosis [74].

The vasculature responds rapidly to aerobic and resistance exercise-induced stimuli, playing a key role in the acute and chronic beneficial adaptations of exercise. The vascular network undergoes significant functional (acute effects) as well as structural (long-term effects) adaptations to adapt to the exercise-induced metabolic demands, which are characterized by significant variations in intensity-dependent hemodynamic stress. In line with this notion, it is thought that vascular shear stress, which is elevated in response to exercise to supply active cardiac and skeletal muscles with blood to meet the increased metabolic demands, seems to be the prime physiological signal that promotes exercise-induced vascular adaptations [75].

Exercise-induced functional adaptations in the vasculature precede structural changes however, both materialize in response to exercise in both the normal population as well as in patients with RA. Nitric oxide is a major vasodilator regulating vascular homeostasis and a molecule that is highly responsive to exercise-induce stimuli. It is also one of the most important molecular adaptations to exercise training that takes place both in the skeletal as well as the coronary vasculature. A systematic review and meta-analysis of 51 randomized controlled trials in healthy adults revealed that aerobic exercise, resistance exercise as well as the combination of these two, all significantly increase the bioavailability of nitric oxide, while dose-dependent (i.e. intensity dependent) adaptations take place in response to aerobic exercise training [75]. Nitric oxide is produced by endothelial nitric oxide synthase in the endothelium, and exercise activates endothelial nitric oxide synthase via Akt phosphorylation [76] and stimulates the expression of neuronal and endothelial nitric oxide synthases in skeletal muscle [49]. In addition, exercise can acutely increase endothelial progenitor cells, responsible for endothelial repair, as well as promote endothelial growth and angiogenesis [77]. Finally, shear stress also results in the overexpression of prostacyclin, an effective vasodilator [49]. These pathways suggest that exercise acts as a stimulus in healthy adults for significant events to take place within the vasculature, potentially contributing to the significant benefits that are seen in response to acute and long-term vascular adaptations (Figure 1).

In line with this, the only available study that investigated the effects of exercise on endothelial function in RA, revealed that significant adaptations occur at both three and six months of combined aerobic and resistance training at both micro- (small vessels) and macro-(large arteries) levels [78]. It is also worth noting that results from two different controlled trials, revealed that although exercise results in beneficial changes in the expression of nitric oxide, no such changes are seen upon treatment with anti-TNF agents in RA [79]. Apart from this established mechanism, that may occur early with exercise training, studies comparing long-term athletes with non-exercising controls report also that exercise results in structural changes of the endothelium, such as expansion in the density of arterioles/capillaries and

improved microvascular collateral formation [80]. These adaptations are thought to follow the aforementioned nitric-oxide alterations, however the exact timeframe by which they take place is currently unknown.

Summary

Aerobic and resistance exercise elicits significant beneficial effects on established CVD risk factors and results in beneficial adaptations in the function and structure of the cardiac and vascular systems. Although many studies in non-RA adults have established this and pointed to several potential explanatory biological mechanisms, the exact pathways in a high-grade, chronic inflammatory environment, such as this of RA, and the time-frame and exercise dosage (intensity, frequency and duration) of aerobic and resistance exercise training remain under-investigated and unclear in the RA population. Yet, these collective beneficial effects of exercise on CVD outcomes as well as other patient- and clinically-important outcomes should be actively considered all along the patient journey, by public health to primary care physicians and rheumatology specialists and their multidisciplinary care teams. Maintenance of sufficient exercise dosage to achieve health-enhancing effects potentially requires a lifestyle change in this population and thus, collaborative partnerships are required with expert behavioural scientists and practitioners that understand the different barriers of people with RA, to tackle the lack of engagement in exercise in this patient population. Much more research is needed in this field, all the way from basic research and appropriately designed clinical trials to implementation research in order to advance this field and position correctly exercise in the overall management of a person with RA.

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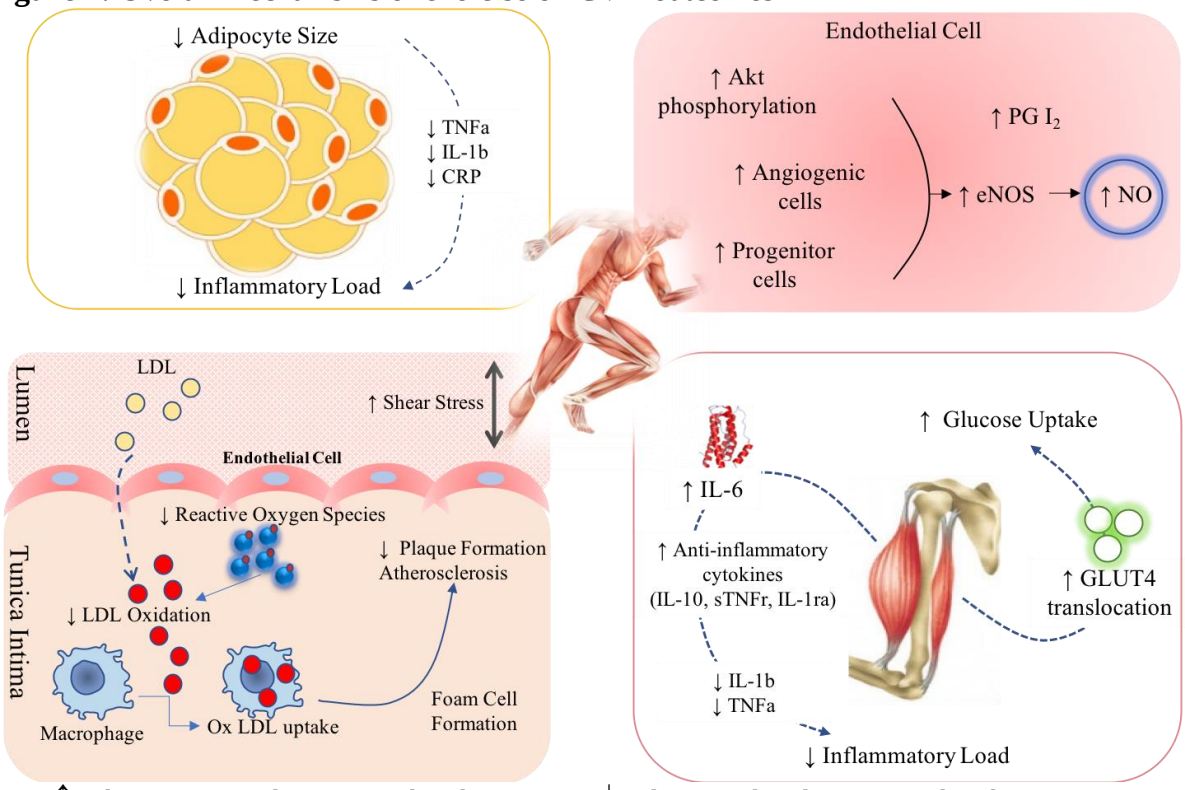
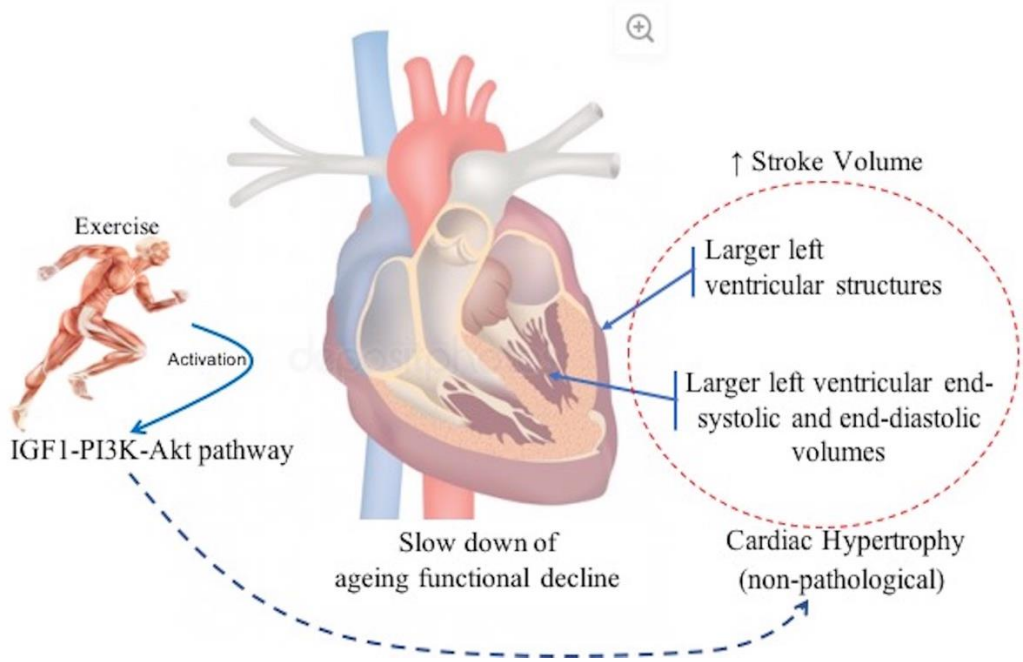
Figure 1: Overall mechanisms of exercise on CVD outcomes



Note: ↑ indicates increased exercise-induced expression, ↓ indicates reduced exercise-induced expression.
Abbreviations: tumor necrosis factor alpha – TNFa, interleukin 1 beta – IL-1b, C-reactive protein – CRP, low-density lipoprotein – LDL, Prostacyclin – PG I_2, endothelial nitric oxide synthase – eNOS, nitric oxide – NO, interleukin 10 – IL-10, interleukin 6 – IL-6, soluble tumor necrosis factor receptors – sTNFr, interleukin 1 receptor antagonist – IL1ra, insulin-regulated glucose transporter – GLUT4.

Figure 2. Exercise-induced functional and structural adaptations



Abbreviations: insulin-growth factor 1 – IGF1, phosphoinositide 3 kinase – PI3K, and protein kinase b – Akt.